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Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF EFAVIRENZ BY CYCLODEXTRIN COMPLEXATION ALONG WITH POLOXAMER 407 AND PVP K30

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Abstract: Efavirenz, a widely prescribed anti retroviral drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. The objective of the study is to enhance the solubility and dissolution rate of efavirenz by cyclodextrin complexation along with Poloxamer 407 and PVP K30 and to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of efavirenz in a series of 2^3 factorial experiments. The solubility of efavirenz in eight selected fluids containing βCD, Poloxamer 407 and PVP K30 as per 2^3 factorial study was determined. βCD alone gave a 3.5 fold increase in the solubility of efavirenz. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 14.08 fold with βCD- Poloxamer 407 and 7.16 fold with βCD- PVP K30. Solid inclusion complexes of efavirenz-βCD were prepared with and without Poloxamer 407 and PVP K30 by kneading method as per 2^3-factorial design and were evaluated. ANOVA indicated that the individual main effects of βCD, Poloxamer 407 and PVP K30 and their combined effects in enhancing the solubility and dissolution rate (K_1) were highly significant ($P < 0.01$). Combination of βCD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K_1) when compared to βCD alone. βCD alone gave 3.98 fold increase and in combination with Poloxamer 407 and PVP K 30, it gave respectively 5.38 and 6.87 fold increase in the dissolution rate of efavirenz. Poloxamer 407 and PVP K30 alone also gave a higher enhancement in the solubility and dissolution rate of efavirenz. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility and dissolution rate of efavirenz a BCS class II drug.
Key**words:** Efavirenz, β Cyclodextrin, Poloxamer 407, PVP K30, Solubility, Dissolution rate, Factorial Study

INTRODUCTION

Efavirenz, a widely prescribed HIV- 1 specific non – nucleoside reverse transcriptase inhibitor drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4,5]. Poloxamer 407 is a polyethylene oxide - polypropylene oxide - polyethylene oxide triblock co-polymer of non-ionic nature and is used as a solubilising agent[6-8]. Poly vinyl pyrrolidone (PVP K 30) is also reported[9, 10] to enhance the solubility and dissolution rate of poorly soluble drugs.

Though cyclodextrin complexation and use of surfactants and PVP for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of efavirenz, a BCS class II drug were evaluated in a 2^3 factorial study.

EXPERIMENTAL

Materials

Efavirenz was a gift sample from M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatham. β Cyclodextrin was gift sample from M/s.

Cerestar Inc., USA. Methanol (Qualigens), poly vinyl pyrrolidone (PVP K30) and Poloxamer 407 were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Efavirenz

A UV Spectrophotometric method based on the measurement of absorbance at 245 nm in water containing 2 % Sodium lauryl sulphate (SLS) was used for the estimation of efavirenz. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.20 % respectively. No interference by the excipients used in the study was observed.

Solubility Determination

Excess drug (50 mg) was added to 15 ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28±1°C) on Rotary Flask Shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µ disk filter. The filtered samples were diluted suitably and assayed for efavirenz by measuring absorbance at 245 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n=4).

Preparation of Efavirenz - βCD Complexes

Solid inclusion complexes of efavirenz – βCD - Poloxamer 407 - PVP K30 were prepared as per 2^3 – factorial study by kneading method. Efavirenz, βCD, Poloxamer 407 and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of water: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Dissolution Rate Study

The dissolution rate of efavirenz as such and from βCD complexes prepared was studied in 900 ml water containing 2 % Sodium lauryl sulphate (SLS) using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1°C was maintained throughout the study. Efavirenz or efavirenz- βCD complex equivalent to 100 mg of efavirenz was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at different intervals of time, suitable diluted and assayed for efavirenz at 245 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

Analysis of Data

Solubility and dissolution data were analyzed by Analysis of Variance (ANOVA) as per 2^3 factorial study.

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of βCD (Factor A), Poloxamer 407 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of efavirenz were evaluated in a series of 2^3-factorial experiments. For this purpose, two levels of βCD (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP K30 (0, 2%) were selected in each case and the corresponding eight treatments involved in the 2^3-factorial study were purified water (1); water containing 5 mM βCD (a); water containing 2% Poloxamer 407 (b); water containing 5 mM βCD and 2% Poloxamer 407 (ab); water containing 2% PVP K30 (c); water containing 5 mM βCD and 2% PVP K30 (ac); water containing 2% Poloxamer 407 and 2% PVP K30 (bc) and water containing 5 mM βCD and 2% of each of Poloxamer 407 and PVP K30 (abc).

Table1. Solubility of Efavirenz in Various Fluids as per 2^3 - Factorial Study

Fluids (Code as per 2^3 - Factorial Experiment)	Solubility (mg/ml) (n=4) ($\bar{x}$) (cv)	Increase in Solubility (Number of Folds)
Distilled water (1)	0.12 (1.2)	-
Water containing 5 mM βCD (a)	0.42 (1.1)	3.50
Water containing 2% Poloxamer (b)	0.53 (0.9)	4.42
Water containing 5 mM βCD and 2% Poloxamer (ab)	1.69 (1.4)	14.08
Water containing 2% PVP (c)	1.17 (0.8)	9.75
Water containing 5 mM βCD and 2% PVP (ac)	0.86 (1.4)	7.16
Water containing 2% Poloxamer and 2% PVP (bc)	1.68 (1.6)	14.0
Water containing 5 mM βCD, 2% Poloxamer and 2% PVP (abc)	1.78 (1.4)	14.83

The solubility of efavirenz in the above mentioned fluids was determined (n=4) and the results are given in Table-1. The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of βCD, Poloxamer 407 and PVP K30on the solubility of efavirenz. The results of ANOVA indicated

that the individual and combined affects of βCD, Poloxamer 407 and PVP K30in enhancing the solubility of efavirenz were highly significant ($P < 0.01$). βCD alone gave a 3.5 fold increase in the solubility of efavirenz. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 14.08 fold with βCD- Poloxamer 407 and 7.16 fold with βCD- PVP K30, than with βCD alone. Poloxamer 407 and PVP K30 alone also gave a significant enhancement, 4.42 and 9.75 fold respectively in the solubility of efavirenz.

Table 2. Dissolution Parameters of Efavirenz-βCD– Pol 407 – PVP K30 Complexes Prepared as per 2^3 Factorial Study

EF-CD Complexes	Composition	PD_{10} (%)	K_1x10^2 (min^{-1})	Increase in K_1 (no.of folds)	DE_{30} (%)	Increase in DE_{30} (no.of folds)
F_1	EF	23.5	1.25	-	30.6	-
F_a	EF - βCD (1:2)	60.0	4.98	3.98	64.8	2.1
F_b	EF - P 407 (2%)	80.9	11.16	8.93	80.18	2.6
F_{ab}	EF - βCD (1:2) - P 407 (2%)	70.7	6.73	5.38	69.86	2.3
F_c	EF - PVP (2%)	81.8	10.01	8.00	70.66	2.3
F_{ac}	EF - βCD (1:2) - PVP (2%)	78.3	8.59	6.87	76.69	2.5
F_{bc}	EF - P 407 (2%) - PVP (2%)	89.8	10.28	8.22	84.45	2.8
F_{abc}	EF - βCD (1:2) - P 407(2%) - PVP (2%)	66.2	7.86	6.29	72.89	2.4

EF - Efavirenz; βCD - Cyclodextrin; P 407 - Poloxamer 407; PVP - Poly vinyl pyrrolidone K 30

To evaluate the individual and combined effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate of efavirenz, solid inclusion complexes of efavirenz- βCD were prepared with and without Poloxamer 407 and PVP K30 as per 2^3-factorial design. For this purpose two levels of βCD (0 and 1:2 ratio of drug : βCD) and two levels of each of Poloxamer 407 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved in the 2^3-factorial study were efavirenz pure drug (1); efavirenz- βCD (1:2) inclusion binary complex (a); efavirenz - Poloxamer 407 (2%) binary complex (b); efavirenz- βCD (1:2) - Poloxamer 407 (2%) ternary complex (ab); efavirenz – PVP K30 (2%) binary complex (c); efavirenz- βCD (1:2) - PVP K30 (2%) ternary complex (ac); efavirenz - Poloxamer 407 (2%) - PVP K30 (2%) ternary complex (bc) and efavirenz-βCD (1:2) - Poloxamer 407 (2%) - PVP K30 (2%) complex (abc).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of efavirenz- βCD - Poloxamer 407 /PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1.2 %) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of efavirenz alone and from βCD complexes was studied in water containing 2 % SLS as prescribed in IP 2010. The dissolution of efavirenz followed first order kinetics with r (correlation coefficient) above 0.9150. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[11]. The dissolution parameters are given in Table-2. The dissolution of efavirenz was rapid and higher in the case of efavirenz-βCD binary and ternary complex systems prepared when compared to efavirenz pure drug as such. The dissolution profiles are given in Fig-1.

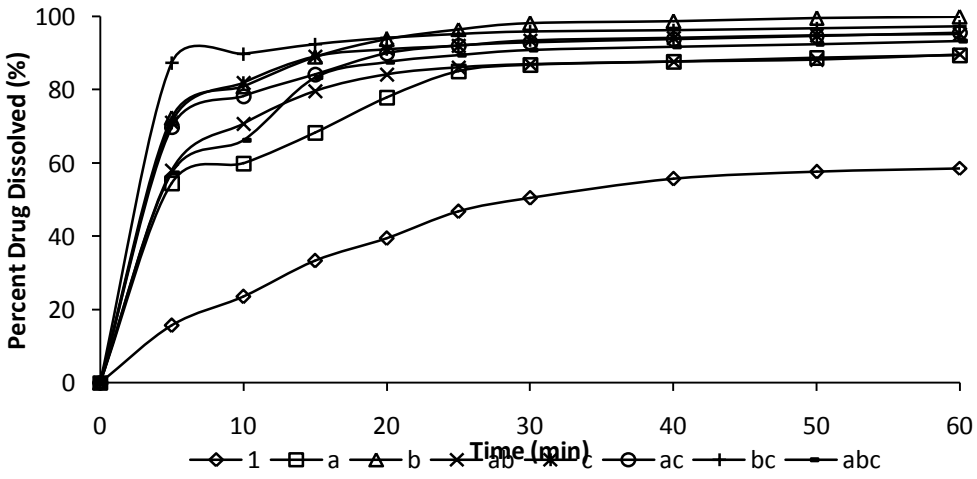

Fig.1: **Dissolution Profiles of Efavirenz – βCD Complexes Prepared by Employing βCD, Poloxamer 407 and PVP K30 as per 2^3 Factorial Design**

The dissolution rate (K_1) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate of efavirenz. ANOVA indicated that the individual main effects of βCD, Poloxamer 407 and PVP K30 and their combined effects in enhancing the dissolution rate (K_1) were highly significant ($P < 0.01$). βCD alone gave a 3.98 fold increase in the dissolution rate of (K_1) of efavirenz. When βCD is combined with Poloxamer 407 and PVP K30 the dissolution rate (K_1) was significantly enhanced. A 5.38 and 6.87 fold increase in the dissolution rate (K_1) was observed respectively with efavirenz- βCD – Poloxamer 407 and efavirenz- βCD – PVP K30 solid inclusion complexes. Poloxamer 407 (F_b) and PVP K30 (F_c) alone and in combination (F_{bc}) also gave 8.0 – 8.9 fold increase in the dissolution rate (K_1) of efavirenz. DE_{30} values were also much higher in the case of βCD – Poloxamer 407 – PVP K 30 solid complexes when compared to efavirenz pure drug.

CONCLUSION

The individual and combined effects of βCD, Poloxamer 407 and PVP K30 in enhancing the solubility and dissolution rate of efavirenz were highly significant ($P < 0.01$). βCD alone gave a 3.5 fold increase in the solubility of efavirenz. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 14.08 fold with βCD- Poloxamer 407 and 7.16 fold with βCD- PVP K30 complexes. Combination of βCD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K_1) when compared to βCD alone. βCD alone gave 3.98 fold increase and in combination with Poloxamer 407 and PVP K 30, it gave respectively 5.38 and 6.87 fold increase in the dissolution rate of efavirenz. Poloxamer 407 and PVP K30 alone also gave a higher enhancement in the solubility and dissolution rate of efavirenz. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility and dissolution rate of efavirenz a BCS class II drug.

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